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TGen Today

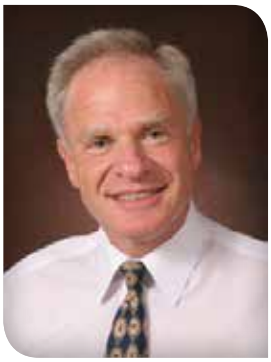
A PUBLICATION OF THE TRANSLATIONAL GENOMICS RESEARCH INSTITUTE

DRIVEN

NASCAR Hopeful Ahnna Parkhurst Races in Support of TGen's Cancer Research and her Mom

tgen

A Non-Profit Biomedical Research Institute



A Look Inside...

Dear Friends,

At TGen, we like to think of the patients we serve as members of our family, and ours is a sprawling bunch that encircles the globe. From children battling neuroblastoma in Lebanon to cancer patients in South Korea, from football players donating blood, urine and saliva samples for concussion research to an army of online test-takers volunteering their time to fight Alzheimer's disease: The TGen family is united in service to one another.

At a time of Thanksgiving, this issue of *TGen Today* celebrates family.

You'll learn of two mothers who refused to give up in their quests for accurate diagnoses for their daughters. Tammy Crawford turned a chance encounter with TGen Physician-in-Chief and Distinguished Professor Dr. Daniel D. Von Hoff into a crusade to develop a more accurate diagnostic test for Lyme disease with scientists at TGen North. Lynnie Morgan searched 37-and-a-half years to find a diagnosis for her daughter Amy, only for TGen's Center for Rare Childhood Disorders to discover that Amy is believed to be the only person in the world to have inherited TCB1D24 mutations from both her mother and father.

You'll meet a spirited teenager named Ahnna Parkhurst. Selected by Richard Childress Racing and Team Dillon as one of two female drivers in their 2015 development program, Ahnna is battling her way through the NASCAR ranks, inspired by her mother Laurie's brave battle against cancer.

You'll learn how TGen scientists are helping families around with world with our innovative "liquid biopsy" research that may predict breast and pancreatic cancer recurrence. This early detection research gives us hope that more mothers and fathers, daughters and sons will give thanks for the gift of more time together.

Finally, we are proud to report that Dr. Von Hoff and an international research dream team of collaborators have been selected for an incredible second award from Stand Up To Cancer. Dr. Von Hoff's continued success can be traced in part to the extraordinary support he receives from TGen's National Advisory Committee for Pancreatic Cancer Research. This is the third Stand Up To Cancer Dream Team that will be led by TGen.

In the spirit of Thanksgiving, the TGen family extends its warmest gratitude to the many supporters who believe in our work; to the patients who trust us to find the answers; and to the caregivers who provide the courage and encouragement to continue onward.

Michael Bassoff
President, TGen Foundation

TGen Today

A Publication of The Translational Genomics Research Institute

About TGen

The Translational Genomics Research Institute (TGen) is a non-profit organization dedicated to conducting ground breaking research with life changing results. Research at TGen is focused on helping patients with diseases such as cancer, neurological disorders and diabetes. TGen is on the cutting edge of translational research where investigators are able to unravel the genetic components of common and complex diseases. Working with collaborators in the scientific and medical communities, TGen is making a substantial contribution to the efficiency and effectiveness of the translational process. For more information, visit: www.tgen.org

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DRIVEN

NASCAR Hopeful Supports Cancer Research

Based on her appearance, driven is not a word one would ascribe to the just-turned 15-year-old Ahnna Parkhurst. That is, until you meet her.

At 5 feet, 6 inches with a slight frame, warm smile, soft blue eyes and flowing blonde hair, she reminds you more of that Disney star you've seen but can't quite place than a high school student with dreams of becoming a NASCAR champion at its highest level. But let the girl from Evans, Georgia, tell you about what she hopes to accomplish in life and you'll soon learn that beneath her pleasant exterior beats the heart of a fighter.

To see her standing next to a 400-horsepower Late Model dirt-track race car that reaches speeds over 100 mph, the scent of oil and fuel rising from the red clay beneath her feet, you might assume she's the daughter of either a driver or one of the pit crew.

Look closely though and you'll notice that *she's* the one wearing the fireproof racing suit and discussing the finer points of suspension set up with *her* crew chief. They both know there is a fine line between winning, placing and finishing somewhere back in the pack. When Ahnna slips behind the wheel, she wants to win. And win. And win.

She's that driven.

And not just when it comes to racing.

She also wants to win against cancer. Emblazoned in pink on the sides of Ahnna's helmet, jacket collar and race car are logos for Laurie's Fund, a campaign to raise money that funds cancer research in honor of her mom, Laurie, who for more than a decade, has waged a remarkable battle against breast, lung and brain cancer.

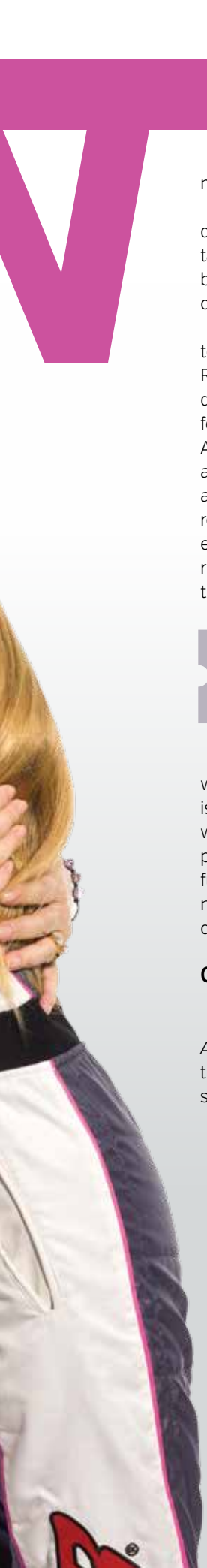
"You're never too young to make a difference," says Ahnna. "Every time I touch the gas pedal, I know I'm just not accelerating

Photos courtesy of professional photographer Brent Cline

my car, but I'm also accelerating the cure for cancer."

Yes, her mother's cancer is a big reason behind her desire to shine a light on the disease, but to hear Ahnna talk about her reasons, it's more than that. It's about beating a disease that kills too many people and impacts countless other lives along the way.

When NASCAR owner Richard Childress named Ahnna to his 2015 development program for Richard Childress Racing and Team Dillon, she moved one step closer to her dream of becoming a professional on the NASCAR circuit, following a similar path to today's NASCAR standouts Austin and Ty Dillon, Kevin Harvick and Clint Bowyer. She also gained a platform that allows her to raise awareness about cancer and much needed funds to support cancer research. Thanks to family connections, Ahnna and the entire Parkhurst family chose to take TGen along for the ride, believing its scientists and doctors are on the right track when it comes to beating all types of cancer.



"Every time I touch the gas pedal, I know I'm just not accelerating my car but I'm also accelerating the cure for cancer." – *Ahnna Parkhurst*

"My mother's struggles with cancer have in many ways been an education for me," says Ahnna. "Cancer isn't something you think about until you know someone who has it. I want to change that. I want to use whatever platform I can to shine a light on cancer and help raise funding to support research. To beat this disease we need people who haven't been affected by it to join the cause as well."

On The Right Track

In the months since its launch, *Laurie's Fund: Accelerating the Cure for Cancer at TGen* has raised more than $111,000 to support the work of the professional scientists and doctors at TGen whose intimate knowledge of molecular medicine is as finely tuned as the suspension system on Ahnna's car.

Technology advancements in recent years now allow TGen scientists to look deeper into the human genome than ever before, which has furthered the research of several faculty members into so-called liquid biopsies – more or less an advanced blood test – for detecting the smallest of cancer cells swimming in a person's blood, looking for a spot to take root and become a full-blown tumor. Finding the cancer early would increase the chance of survival; such tests may also help predict the chance of relapse (see related stories on pages 6 and 20). The funds also support TGen's work into genomics-guided treatment, or using a patient's DNA to better understand his or her cancer, with the resulting information providing guideposts for treatment choices.

"When I hear about what the scientists at TGen are doing I can't help but sense they feel a similar type of adrenaline rush when things work out that racing provides me; we both want to get to the finish line first," says Ahnna. "It's pretty cool and amazing to think that one day a few drops of blood might save a person's life. It's also very humbling to think that Laurie's Fund will have played a role in its success."

For Ahnna, each race provides an opportunity for victory, brings her a step closer to fulfilling her NASCAR aspirations, and increases the exposure to Laurie's Fund. For her mom, Laurie, it brings a great sense of pride.

When you meet Laurie you quickly see how genetics has played a role in Ahnna's drive to win; clearly she handed down the fighter gene to her daughter, a trait evident by the fact that Laurie herself has endured numerous treatments to keep her cancers in check. An 11-year cancer survivor, Laurie has undergone 20 types of chemotherapy, multiple surgeries, full and half-brain radiation treatments, and 5 Gamma Knife procedures, yet through it all she has maintained a positive outlook.

"With every race, Ahnna raises awareness and research dollars for the physicians and scientists at TGen," says Laurie, whose resolve has always been to 'Be The Miracle.' "I have decided to claim that victory. As long as I am able, I will fight this disease in hopes to win the war, not just the battles, set before me."

Throughout the ups and downs of Laurie's battles with cancer, racing has remained a family affair. Ahnna's 13-year-old sister, Sophia, is her business manager. Her father – and Laurie's high-school sweetheart – Michael, chief support officer.

"We are supportive of the efforts at TGen, which we hope will find answers for the millions of patients battling cancer," said Michael, who recently organized a fund-raising effort around Laurie's birthday.

Those answers will come.

Former NASCAR driver Janet Guthrie once said racing is a matter of spirit not strength, and that is a line quite apropos to all that both Ahnna and TGen hope to achieve. Until then it's pedal to the metal because there are races to run and progress to make.

Learn more about Laurie's Fund by visiting
www.tgen.org/LauriesFund

Altering Pancreatic Cancer's Plan

SU2C Dream Team looks to reprogram the biology driving tumor growth

TGen's pancreatic cancer team: (L-R) Dr. Daniel D. Von Hoff, Dr. Haiyong Han, Ruben Munoz, Serina Ng, Maria Nicolas-Perez, Jennifer Harper. Not pictured is Tiffanie Cappello Lee.

TGen will lead its third Stand Up To Cancer (SU2C) Dream Team, and its second SU2C Dream Team aimed at a fresh attack on the deadliest of all malignancies: pancreatic cancer.

Dr. Daniel D. Von Hoff, TGen's Physician-in-Chief and Distinguished Professor – considered one of the world's leading authorities on pancreatic cancer – will lead the project's international team of top cancer researchers from the United States and United Kingdom.

"Our overarching aim is to develop therapies that at least double a person's survival," Dr. Von Hoff said. "In this project, we will pursue pancreatic cancer in a different way than ever before. We will focus on reprogramming the master machinery in cancer cells that drive tumor growth. Our targets are the complexes of DNA and proteins known as 'super enhancers' for their ability to affect a large number of genes."

After a rigorous selection process, SU2C, Cancer Research UK and The Lustgarten Foundation Fund selected the team and will provide the project's $12 million funding over three years.

TGen's new Pancreatic Cancer Dream Team was announced Nov. 6 in Boston during the 2015 International Conference on Molecular Therapeutic Targets and Cancer Therapeutics, sponsored by the American Association for Cancer Research (AACR), the National Cancer Institute, and the European Organization for Research and Treatment of Cancer. The AACR is SU2C's scientific partner and will administer the grant.

Ronald M. Evans, PhD, Professor and Director of the Gene Expression Laboratory at the Salk Institute for Biological Studies in La Jolla, Calif., and Gerard I. Evan, PhD, Professor and Chair of the Department of Biochemistry at the University of Cambridge, U.K., are the project's co-leaders.

Serving as principal investigators on the team are Christopher Heeschen, MD, PhD, lead, Centre for Stem Cells in Cancer & Ageing at the Barts Cancer Institute, Queen Mary University of London, U.K.; David Propper, MD, a consultant medical oncologist at Barts Cancer Institute and the London NHS Trust; and Joshua D. Rabinowitz, MD, PhD, professor of chemistry and integrative genomics at Princeton University.

The team also includes more than two-dozen other researchers based in the U.S. and the U.K., and two advocates, Suzanne Berenger of England, and Howard Young of the United States, both of whom are pancreatic cancer survivors. Young, an Atlanta businessman and a Board Member of the TGen Foundation, credits TGen and Dr. Von Hoff with saving his life.

The new Dream Team's research will focus on reprogramming the biology of cells in pancreatic tumors – both the cancer cells themselves as well as the surrounding non-cancerous cells upon which the cancer cells rely for support – so that the tumors can be stopped.

They have found biological pathways in pancreatic tumors controlled by areas in the DNA called "super enhancers" (SEs) that are similar to those in injured tissues where repair and regenerative mechanisms are essential to restore normal function. Unlike the normal system of wound healing that has a shut-off mechanism, in tumors the process remains on, "hijacked" to constantly drive growth. Another way to look at it is the normal wound-healing process is hacked to produce the cancer.

> "As devastating as these statistics are, they don't begin to describe the considerable pain and suffering associated with this disease."

Pancreatic cancer has a dismal outlook, with a five-year survival rate of less than 10 percent, the worst of any cancer. Each year, it takes the lives of more than 40,000 Americans, making it the fourth leading cause of cancer death in the U.S.

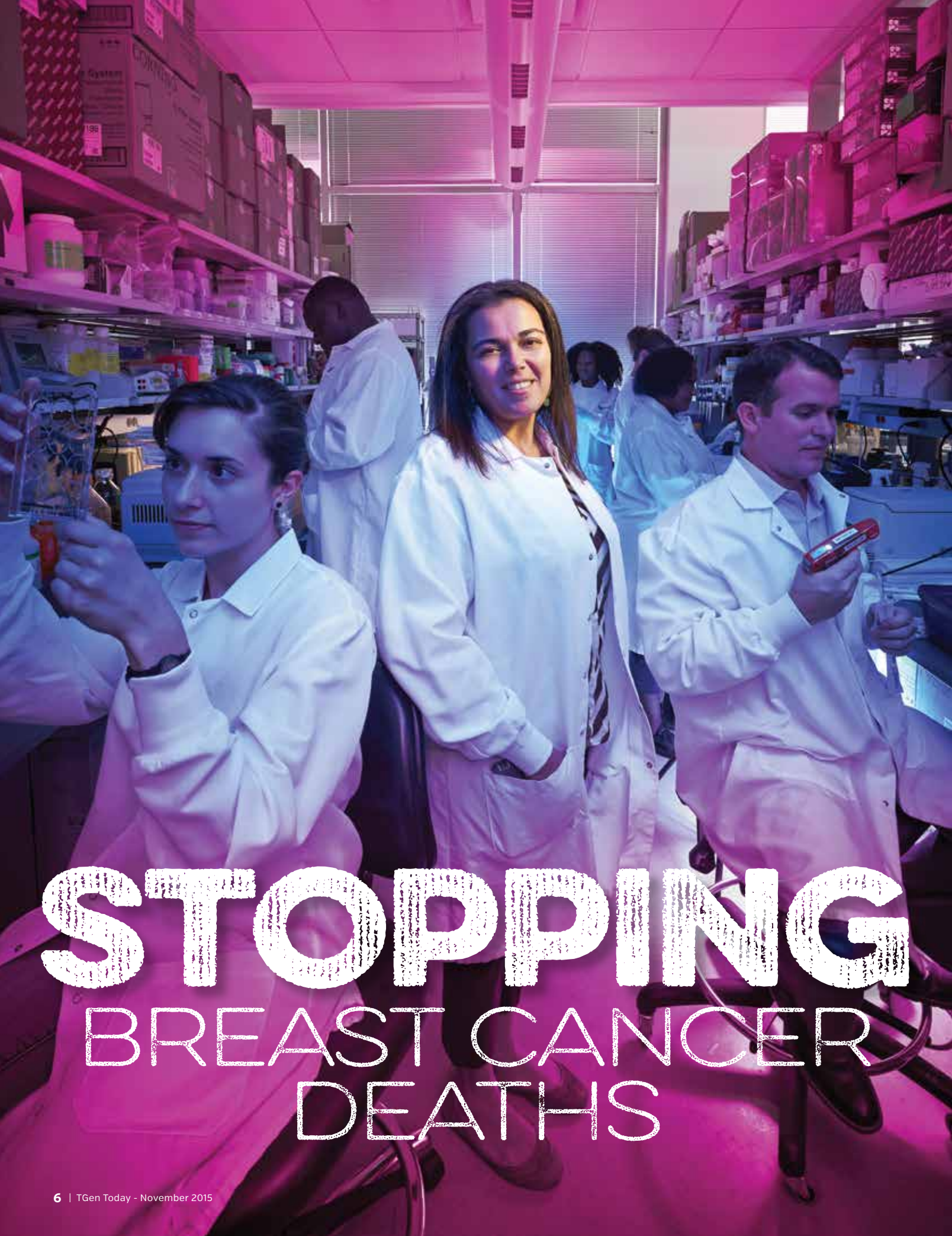
"As devastating as these statistics are, they don't begin to describe the considerable pain and suffering associated with this disease," said Dr. Von Hoff. "Our team brings together the very best experts on both sides of the Atlantic, and we feel confident that we will soon bring better treatments to the patients that need our help today."

A major part of the study will be taking drugs that target super enhancers, as well as combinations of SE drugs with chemotherapies and immunotherapeutic drugs, into clinical trials within the first year of the study. Clinical trials are planned in Arizona, Pennsylvania, San Diego and the U.K.

"Cancer is a like a wound that does not heal," Von Hoff said. "We think the control of healing happens through super enhancers, and in cancer that control mechanism is malfunctioning. We hope to reboot the super enhancers and send the pancreatic cancer into durable remission."

In 2009, TGen was selected to lead one of the first SU2C Dream Teams. It also was supervised by Dr. Von Hoff and also focused research on pancreatic cancer. That work resulted in a treatment regimen that has produced some long-term survivors of this disease.

In 2011, TGen was named to lead a SU2C Dream Team, in association with the Melanoma Research Alliance, aimed at addressing unmet needs of melanoma patients. A nationwide set of clinical trials stemming from this project's research began earlier this year.



STOPPING BREAST CANCER DEATHS

Will it spread? Will it come back? New research may predict patients' future, answer questions

You have breast cancer, but it's in its early stages. You've had surgery. You've had radiation treatment. You've had chemotherapy. There is a good chance that your cancer will not return, but your doctor cannot tell you that with certainty.

And while treatments have vastly improved in recent years for the more than 234,000 American women who annually develop breast cancer, it remains impossible to tell – even for the most treatable types of the disease – whether the cancer will remain in remission, return to the original site, or worse, mutate and spread to a distant organ such as the liver, lungs or brain.

It is this spreading, or metastasis, that is responsible for most of the nearly 41,000 annual breast cancer-related deaths in the U.S.

The results of a recent study led by TGen's Dr. Bodour Salhia may soon tip the scales in favor of the patient by removing much of the guesswork when predicting a risk of recurrence or metastases.

Dr. Salhia and her colleagues identified 21 DNA hypermethylation hotspots, or gene locations along an individual's 3 billion chemical bases of DNA, with increased levels of methylation that could indicate the existence of metastatic breast cancer. These findings could lead to a highly sensitive blood-based test panel (a type of liquid biopsy) that could help predict relapse in women with breast cancer.

This 21-gene signature is a potential biomarker that could indicate patients who are at high risk of cancer recurrence, either in the breast or elsewhere in the body, and who might benefit from additional therapy to eliminate the potential of recurrence. Biomarkers are indicator molecules, such as proteins or DNA, that are measurable in blood, body fluids or tissue samples and can be used to diagnose or measure a particular disease or the effects of a given treatment.

"Once therapy is completed, women – and their oncologists – often still don't know what their risk of recurrence is," Dr. Salhia said. "Because we are able to detect a unique signature in metastatic breast cancer patients that doesn't exist in healthy individuals, or in patients who have been in remission for many years, we want to use this information to develop a test that will help physicians more accurately address this question."

> "To be able to detect cancer in the blood, predict in which patients the cancer will recur, that would be fantastic."
>
> – *Dr. Bodour Salhia*

This test would rely on TGen's mastery of gene sequencing and follows TGen's growing efforts to create methods of early cancer detection.

To further validate the predictive power of this 21-gene panel, Dr. Salhia is collecting samples from a prospective clinical trial with colleagues at Mayo Clinic Arizona, with additional trials under consideration with partnering institutions. As many as 100 breast cancer patients in the Mayo trial will be enrolled and monitored over the next several years. If the trial results correlate with patients who relapse or show signs of metastasis, the researchers will be a step closer to confirming the effectiveness of the biomarker.

A significant advantage of this test is that rather than rely on invasive tissue biopsies (a small surgical procedure to collect tissue to determine the presence or degree of cancer), usually available at a single point in time, it measures circulating tumor DNA (ctDNA) garnered from blood samples.

"The idea is to take the 21-gene signature that we associated with metastatic breast cancer in the blood of these women, and develop it into a predictive marker that we can use when women still have early stage breast cancer, so well before metastatic disease becomes symptomatic and a clinical dilemma," Dr. Salhia said.

The research discovery offers significant promise for all breast cancer patients in the future. It could provide physicians with critical information about the need for additional therapies, especially following surgery or sessions of chemotherapy.

"Once a woman develops Stage 4 metastatic breast cancer, managing the disease becomes difficult and, unfortunately, the survival rate plummets," Dr. Salhia said. "Maybe therapies would be successful it they were given a lot sooner, rather than at Stage 4."

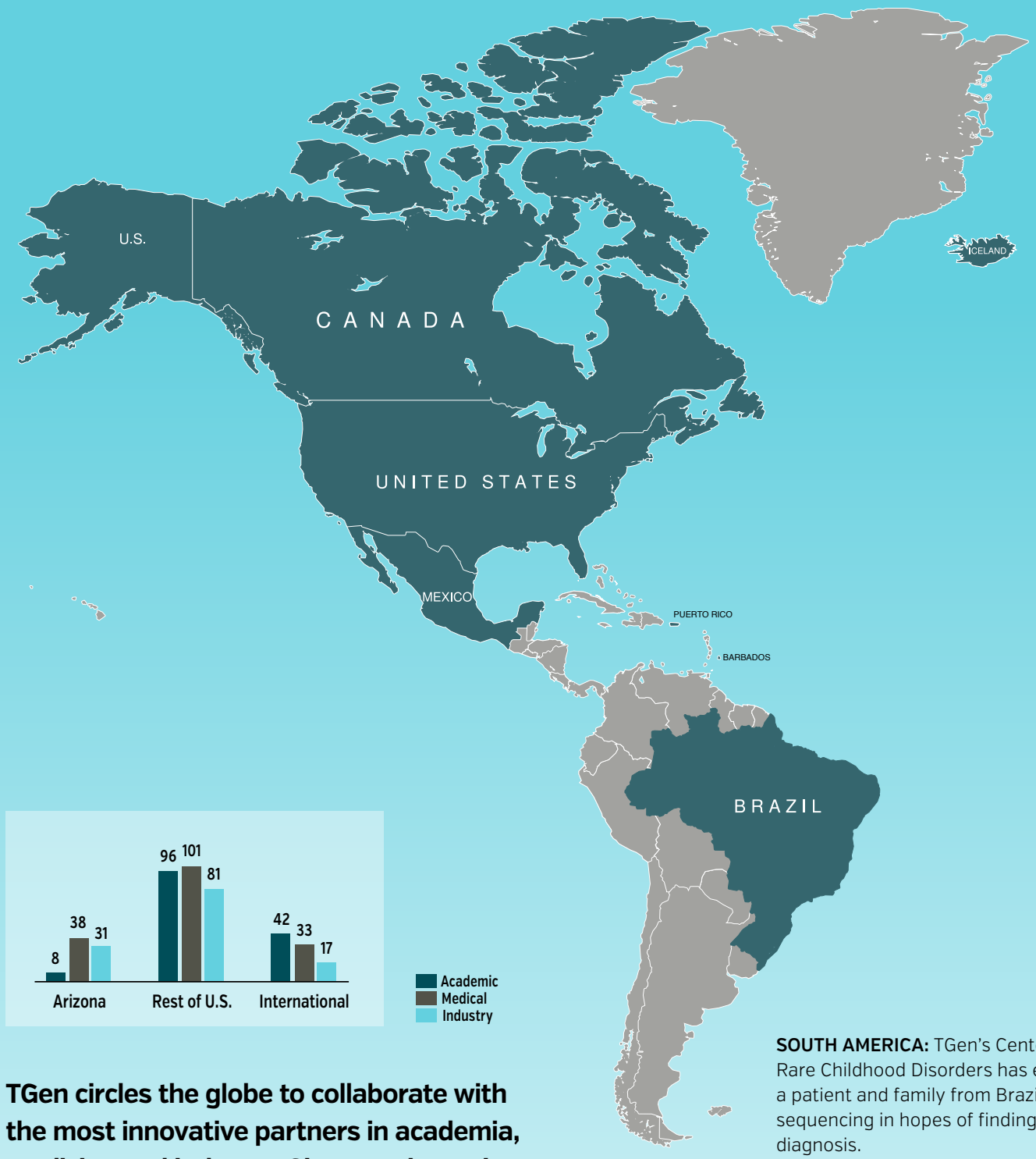
The test looks for epigenetic alterations, chemical changes to DNA that do not affect its sequence.

As the prospective trials continue, researchers will work to refine the test, to make it highly sensitive and highly specific.

Another goal is to look specifically at breast cancer that metastasizes to the brain, because the especially small blood vessels that surround the brain allow the cancer cells to penetrate, but reject larger chemotherapy molecules. In essence, these cancer cells can find a sanctuary in the brain.

"To be able to detect cancer in the blood, to be able to predict in which patients the cancer will recur, that would be fantastic," Dr. Salhia said. "If we can do that, then we could really try to eradicate the mortality associated with breast cancer. I think this kind of precision diagnostics is going to be so critical to improving the overall outcomes for breast cancer patients."

The Sun Never

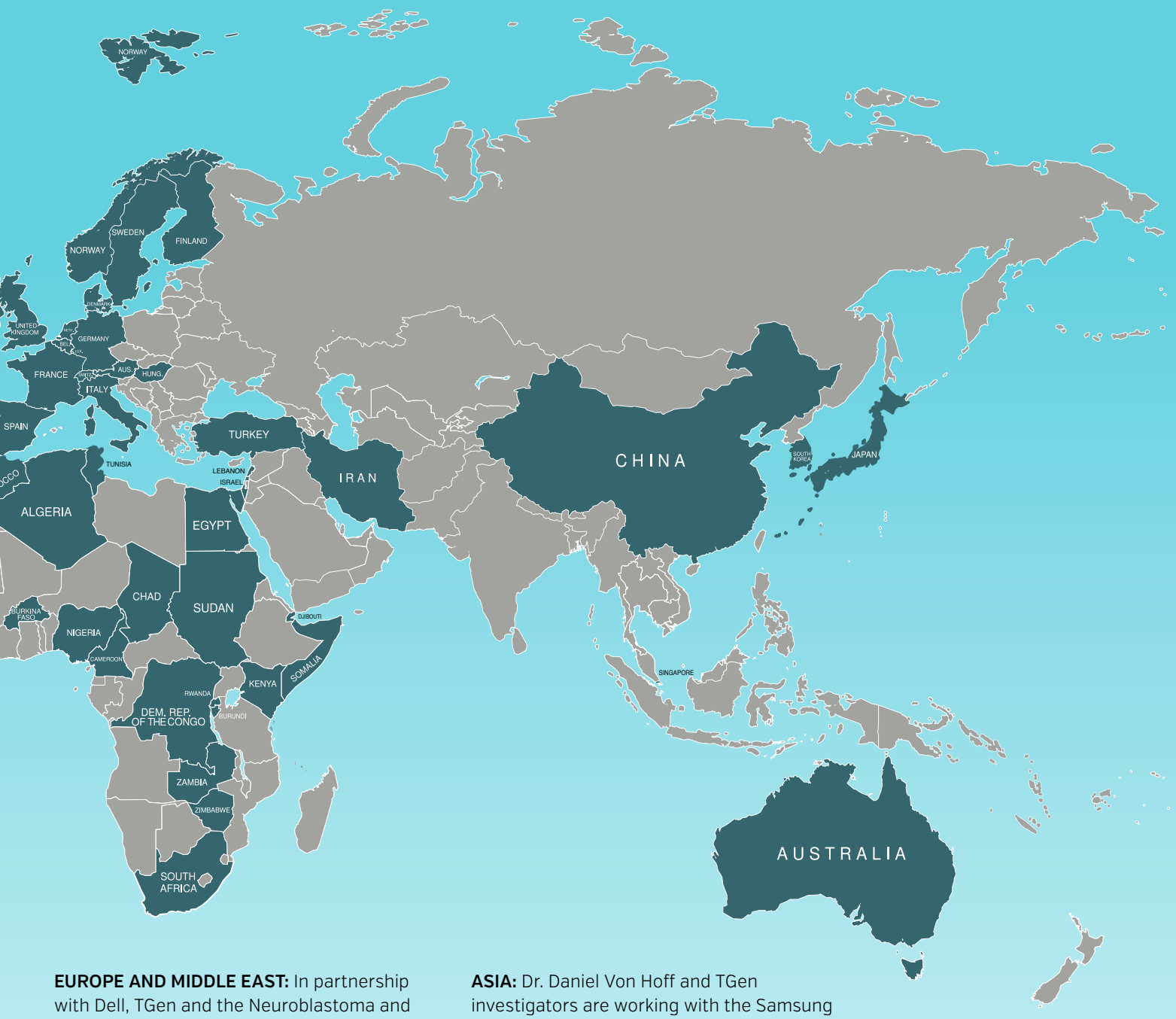


TGen circles the globe to collaborate with the most innovative partners in academia, medicine and industry. Since our inception, TGen scientists have worked on more than 440 projects on six continents in 28 countries and U.S. territories. Highlights Include:

SOUTH AMERICA: TGen's Center for Rare Childhood Disorders has enrolled a patient and family from Brazil for sequencing in hopes of finding a diagnosis.

EUROPE: Dr. Lance Price at TGen North along with the Statens Serum Institute of Denmark, Amphia Hospital of The Netherlands, and Kent State University are investigating a new type of MRSA and developing a rapid genotyping system to study this pathogen.

Sets on our Work



EUROPE AND MIDDLE EAST: In partnership with Dell, TGen and the Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC) are expanding the first FDA-approved precision medicine trial for pediatric cancer, starting with sites in France and Lebanon.

AFRICA: People from 146 countries have taken the MindCrowd online memory quiz to support our Alzheimer's disease research. Included in this number are 188 people from 18 African nations.

ASIA: Dr. Daniel Von Hoff and TGen investigators are working with the Samsung Medical Center in South Korea on genomic-based clinical trials.

AUSTRALIA: TGen president Dr. Jeffrey Trent, Dr. Nicholas Hayward at the Queensland Institute of Medical Research, and their teams in the U.S. and Australia study the genetics of susceptibility to melanoma.

(L-R) Amy Morgan and Keri Ramsey, Clinical Manager for TGen's Center for Rare Childhood Disorders

37-YEAR MYSTERY SOLVED

After 37-and-a-half years of questions, the Morgan family gathered around their kitchen table for a definitive answer from Newell Belnap, Clinical Research Coordinator for TGen's Center for Rare Childhood Disorders.

Kevin and Lynnie Morgan learned that their daughter Amy has two rare mutations located on the gene TBC1D24. Amy is believed to be the only person in the world known to have inherited these mutations from both her mother and father.

"For me, it was the end of a journey. I cried for 15 minutes straight," Lynnie explained. "Every year, for 37 years, there were always those questions in the back of my mind: What if we're treating her for the wrong thing? What if there's a better treatment out there? For me, a diagnosis means I don't have to look anymore. I don't have to wonder if I'm doing the best for my child."

Those questions started when Amy was 3 months old: Sometimes she'd sleep all day and be up all night, or sleep half the day and half the night. She'd have bouts of crying, screaming for hours on end, jerking her arms and legs nonstop. Doctors told Lynnie that Amy looked fine, that her schedule would work itself out eventually, that it was normal.

"We switched doctors after the first one told me I was just a neurotic first-time mother," Lynnie recalled. "He said I should just go home and have a glass of wine."

Then on June 30, 1978 – one month before Amy's first birthday – Lynnie ran into the doctor's clinic, screaming for help as her baby seized in her arms. It was the start of a 37-year diagnostic odyssey for the Morgan family.

From their home in northern California, Kevin and Lynnie took Amy to more than 400 doctors and specialists around the country, seeking answers for her seizures, developmental disabilities, balance and movement issues. Exotic diagnoses came and went – Parkinson's disease, mitochondrial encephalomypathy, Segawa disease – but nothing quite seemed to fit. According to Global Genes, a genetic disease advocacy organization, rare disease patients will visit an average of 10 specialists, be misdiagnosed three times and search eight years before finding a diagnosis.

The whole family went on this journey with her: Amy has a brother Shea, 36, who is a carrier for one of the mutations and shows no symptoms. They have two adopted siblings, Brenna, 30, and Joseph who died in 2010. Through it all, Amy enrolled in educational day programs and mainstreamed into some classes at school. She attended camp for disabled young people. They tried to live a normal life, despite the lingering questions.

In 2014, Lynnie and Amy attended a training program for a new service dog at Canine Companions for Independence in Santa Rosa, Calif. There, Lynnie met another mom whose son had just received a diagnosis from TGen's Center for Rare Childhood Disorders.

"And she said, 'if you're looking into genetics, you'll want to know about a place in Arizona called TGen,'" Lynnie recalled.

Roughly 80 percent of all rare disorders have genetic origins, according to Global Genes, so sequencing through the Center can often provide that elusive answer. Afraid Amy might not qualify due to her

age, Lynnie sent an email to the Center that night. She was surprised at the warm, respectful reception she received.

"We have a first-hand look at how these families have experienced test after test with no answer," explained Keri Ramsey, Clinical Manager for the Center. "We want to help more than anything, even if that's just embracing a family when we don't have a diagnosis. We want to support them because they've been through so much."

Kevin, Lynnie and Amy submitted DNA samples to the Center in March 2014 and received a definitive diagnosis in March 2015. In May, they came to the Center to give skin samples, which will help scientists understand more about Amy's mutations and investigate new treatment options.

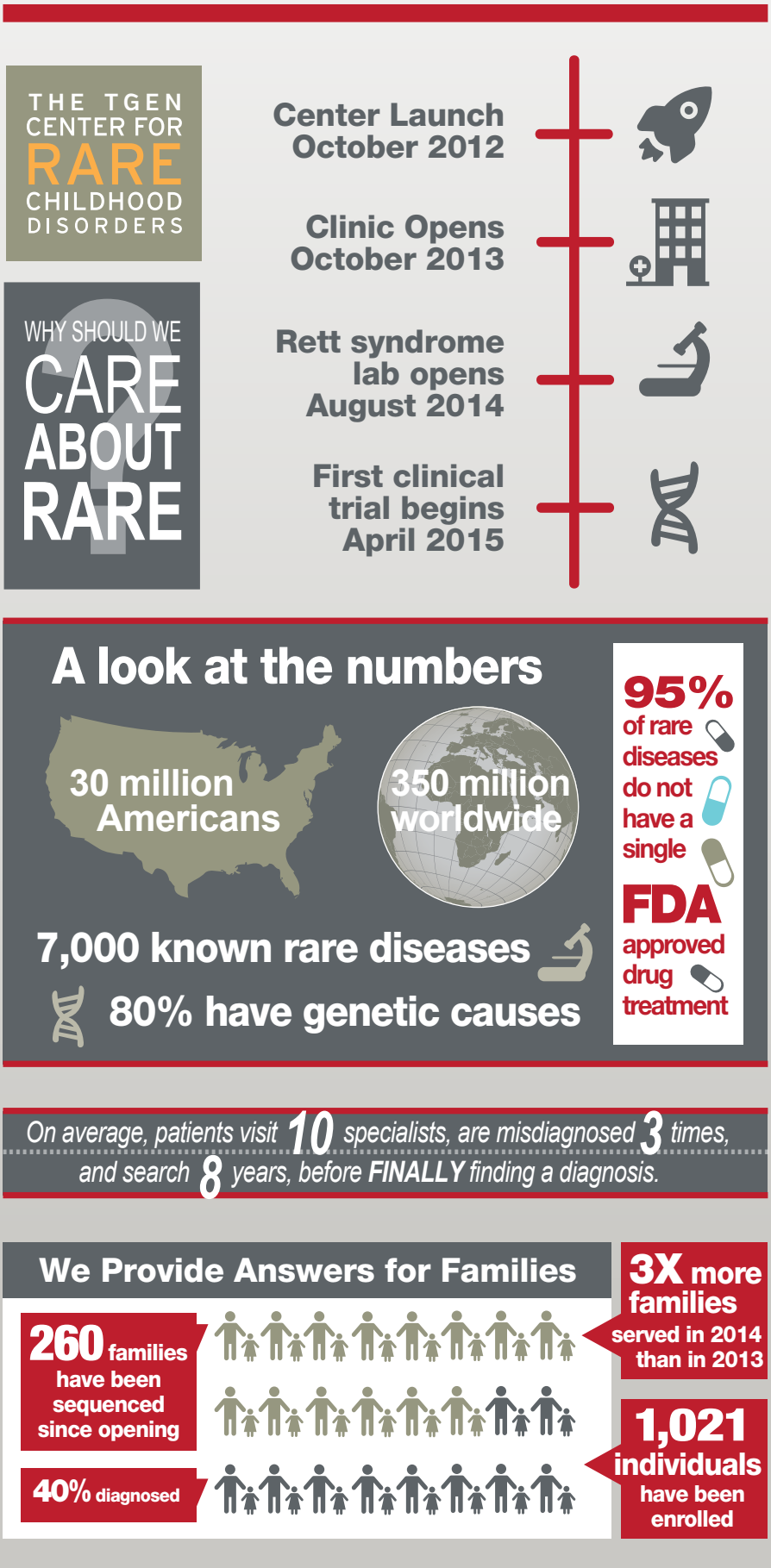
TGen scientists pored over billions of data-points that emerged from the family's DNA to bring an end to their questions. Mathematical algorithms pointed to some possibilities, but it was the clinical knowledge of Amy's symptoms that would lead the Center's co-directors Dr. David Craig and Dr. Matt Huentelman, medical director Dr. Vinodh Narayanan and their team of clinicians, bioinformaticians and researchers to solve the mystery.

"It's kind of like that TV show *House* where everyone is sitting around the table throwing out ideas," Keri explained. "There are less than 10 families published in the literature who have mutations in TBC1D24 and symptoms similar to Amy's. Even though it's such a rare syndrome, the data lined up with Amy's clinical picture. It was one of those 'Eureka!' moments for the team."

The Center contacted Dr. Phillippe Campeau in Montreal, the world's leading authority on TBC1D24, and connected him with Amy's family to collaborate further.

For Lynnie, the answer to a 37-year-old question has brought peace to her family and rewarded their faith.

"I trust in a loving God and He has kept me sane and kept us motivated through all this," Lynnie explained. "We were listening to a speaker. At the end of the talk, Amy leaned over crying on my shoulder and said, 'Mom, thank you so much for finding out what I have.'"



When Disease Gets This Personal, So Do We.

(L-R) The Crowell Family: Gianna, Dave (dad), Isaac, Emilia, Ethan, Deacon, Mary (mom)

Arizona Family Finds Answer to Diagnostic Puzzle

at TGen's Center for Rare Childhood Disorders

Emilia Crowell's family searched for years to find reasons why their otherwise energetic and playful daughter was so thin, was unable to retain fat and appeared older than her age.

Then they found TGen's Center for Rare Childhood Disorders, which examines the genetic basis of disease in children with medical conditions that have no definitive diagnosis.

And everything changed.

Like so many families with children who have undiagnosed medical conditions, Emilia's family went from doctor to doctor, hospital to hospital, across the nation to find answers.

The Tempe, Ariz., girl presented to doctors with pulmonary hypertension, a form of high blood pressure that affects the heart and lungs. She had a feeding disorder and was failing to thrive. In addition, she had symptoms of lipodystrophy, a medical condition characterized by a severe loss of body fat, in which patients can develop insulin resistance, diabetes, high triglyceride levels, and fatty liver.

"It was like a marathon trying to figure out, 'What is this? What are the underlying causes of what's happening to her?' We needed to find out, but no one could tell us why," said Emilia's mother, Mary Crowell.

Dr. Vinodh Narayanan, Medical Director of TGen's Center, suggested that Emilia and her family were good candidates for genetic sequencing, in which the 3 billion bases of DNA are spelled out.

TGen diagnosed her appearance of premature aging as a neonatal form of Progeroid syndrome caused by a mutation in the gene CAV1. This gene codes for caveolin 1, a key protein in the plasma membrane of individual cells that helps regulate many cellular functions.

Researchers also found that Emilia's lack of body fat could be due to the cumulative combination of the defective functions not only of the CAV1 gene, but also of the LPIN1 and AGPAT2 genes, according to a TGen study published in July in the journal *PLOS ONE*.

"It was like a light bulb switched on," said Mary. "Wow! We are actually going to figure this out. TGen was able to identify the genetic errors that were likely causing all of her symptoms."

Now that the family has answers, they are better equipped to help manage her unique medical conditions.

"This case may contribute to a better understanding of the pathogenic mechanisms that contribute to the severe reduction of body fat, the appearance of premature aging, as well as the serious medical problems that affect Emilia," said Dr. Narayanan. "Such understanding may lead to better approaches to her treatment, and allow us to anticipate, detect and treat complications before they become severe."

Mary Crowell has high praise for the way TGen staff collaborates with the family and brings together expertise from other institutions.

"The Center's willingness to work with parents is honestly something we have not found anywhere else," she said. "The ease with which they share information with other labs is so important to the progress, and in our case imperative to the life and wellbeing of our daughter. TGen really leads the way."

Dr. Matt Huentelman, Co-Director of TGen's Center, said having a diagnosis is a major step in the continuing care of patients. "This is a unique discovery and a prime example of how children born with rare, undiagnosed conditions may benefit from a diagnosis obtained through genetic sequencing."

Since it was established in 2012, TGen's Center has enrolled 1,021 participants and analyzed the genomes of 260 families, with a diagnostic success rate of nearly 40 percent, nearly triple the average diagnostic success in such cases.

"Emilia is a bright, energetic little girl and shows no signs of neurological problems," said Dr. Isabelle Schrauwen, a Research Assistant Professor in Dr. Huentelman's lab and the lead author of scientific paper. "We really owe a debt of gratitude to her, her family, and all of the families who work with us at the Center. Without their commitment to research, we wouldn't be where we are today."

Emilia Crowell had her DNA sequenced and TGen was able to identify the genetic changes that were likely causing of her symptoms.

ANOTHER TGEN FIRST

Gene mutation associated with brain and eye disorders is discovered

TGen has identified a genetic mutation responsible for a debilitating childhood neurological condition known as Aicardi syndrome.

Researchers at TGen's Center for Rare Childhood Disorders identified mutations to a gene known as TEAD1, which not only affects formation of the brain but also the retina, the part of the eye responsible for helping turn light into nerve impulses.

"Discovering the first gene mutation associated with Aicardi syndrome is a revolutionary finding with many implications about how children with this disorder might be best identified and treated in the future," said Dr. Matt Huentelman, Co-Director of TGen's Center.

Within five months of birth, children with Aicardi syndrome experience spasms or seizures; ice-cream-scoop-like divots in the retina known as chorioretinal lacunae; and a partial or complete absence of a key brain structure called the corpus callosum, which normally connects the two sides, or hemispheres, of the brain.

To identify genetic factors in the cellular pathways involved in Aicardi, TGen researchers sequenced the genomes of 10 children with the disorder, as well as their parents. By screening the billions of pieces of genetic information, they discovered a mutation in TEAD1.

TGen also found that – contrary to previous studies – Aicardi syndrome may also occur in boys, as well as girls. Aicardi might also be more common among boys than previously thought because the TEAD1 mutation is on an autosome, a chromosome not linked to sex, according to a TGen study published in June in the scientific journal *Investigative Ophthalmology & Visual Science*.

Aicardi had been strongly presumed by geneticists to be an X-linked-dominant disorder occurring almost exclusively in females. However, no gene on the X chromosome has ever been conclusively associated with Aicardi.

TGen's Center for Rare Childhood Disorders is headed by three TGen scientists: Medical Director Dr. Vinodh Narayanan, and Co-Directors Dr. Huentelman and Dr. David Craig, who also is TGen Deputy Director of Bioinformatics. For information about TGen's rare-disorders program and clinic, please visit: www.c4rcd.org.

More than a Coincidence?

Chance encounter leads to Lyme disease test

(L-R) TGen North Director Dr. Paul Keim, Jessica Crawford and her mother Tammy Crawford

A chance airline encounter between TGen's Physician-in-Chief, Dr. Daniel Von Hoff, and the mother of a young woman with Lyme disease has led TGen's Pathogen Genomics Division to begin development of a new and exacting test for this debilitating illness that affects nearly 300,000 Americans each year.

After sharing family medical stories with Tammy Crawford – whose daughter, Jessica, was stricken with Lyme disease in 2012 – Dr. Von Hoff put Tammy in touch with TGen North Director Dr. Paul Keim.

"I felt like this was just meant to be," said Tammy, Executive Director of Focus On Lyme, a Gilbert, Ariz., organization that in July gave TGen $75,000 to develop a new genetic-based test for Lyme that would be quick, affordable and – above all – accurate.

Current tests for Lyme disease are so unreliable that Tammy likens them to no better than a coin flip.

Instead, scientists at TGen North in Flagstaff, Ariz., will use the power of targeted DNA sequencing to develop and validate a test at the genomic level to measure the presence and severity of tick-borne Lyme.

By analyzing DNA from a patient's blood, the new test should be able to pinpoint Lyme disease, identify multiple Lyme strains, detect other tick-related infections, and show non-Lyme causes of disease.

"With recent advances at TGen and genomics overall, we can finally develop a diagnostic test that will put more actionable information into the hands of the physician than previously possible," said Dr. Keim, who also is Director of the Center for Microbial Genetics & Genomics at Northern Arizona University (NAU), which will help develop the test.

In addition to helping fund TGen's development of a new test, Focus On Lyme plans an inaugural Scientific Conference about Lyme disease Feb. 11-13, 2016. This invitation-only event will bring researchers and clinicians together to discuss diagnosis and treatment for Lyme patients.

Focus On Lyme will hold a public fundraising dinner on Feb. 12, 2016, at the Omni Scottsdale Resort & Spa at Montelucia. Proceeds will assist clinical assessment leading to FDA approval of TGen's diagnostic tool.

The bacterium that causes Lyme disease occurs naturally in mice, squirrels and other small animals. The infection spreads as ticks feed on these animals and then bite humans.

This infection can manifest with a bulls-eye rash or a non-specific rash, but not always. Flu-like symptoms, such as fever, headache, body aches and fatigue can last a few days to a few weeks.

If detected early, most cases of Lyme disease can be successfully treated with antibiotics.

Undiagnosed and untreated cases can lead to fatigue, painful and swollen joints, memory loss, insomnia, heart palpitations, difficulty with concentration and other changes, including those that mimic other diseases, complicating a clinical diagnosis.

This is why an accurate diagnostic tool is essential.

Rapid Detection is on the Horizon

CLINICAL TRIALS BEGIN FOR VALLEY FEVER TEST DEVELOPED BY TGEN NORTH

The infectious pathogen that causes Valley Fever is as much a part of the Arizona landscape as scorpions, snakes and saguaros.

A fungus called *Coccidioides* causes Valley Fever, and the most common way people are infected is by simply breathing in the desert dust.

While most people do not develop significant symptoms, a number of those infected develop highly debilitating symptoms, such as cough, fever and fatigue. Creating an early, definitive diagnostic is critical to patient health, since these symptoms are similar to other respiratory diseases caused by bacteria or viruses. As a result, Valley Fever is often misdiagnosed and mistreated.

In August, DxNA LLC, a private company based in St. George, Utah, announced the start of a multi-center clinical study of a molecular diagnostic test for the detection of Valley Fever that was developed by scientists at TGen North in Flagstaff, Ariz.

"Valley Fever is Arizona's disease and therefore has always been a critical target for TGen," said Dr. Paul Keim, Director of TGen North. "This is an exciting step towards the realization of our Valley Fever diagnostic test being able to help clinicians better diagnose and respond to patients."

DxNA intends in 2015 to submit its 510(k) application to the U.S. Food and Drug Administration for clearance of the test and its proprietary diagnostic platform, The GeneSTAT® System. The Valley Fever test on the GeneSTAT System, which will provide for the rapid detection of the fungus in patients, was developed based on intellectual property exclusively licensed from TGen.

Currently, definitive testing for Valley Fever is done by culture, growing the fungus in a laboratory. This process is time consuming, up to 21 days, and potentially exposes laboratory personnel to the highly infective fungus. The highly sensitive DxNA test is performed directly on the patient specimen, reducing the time to a definitive diagnosis and appropriate care.

Key to the Cure at Saks Fifth Avenue

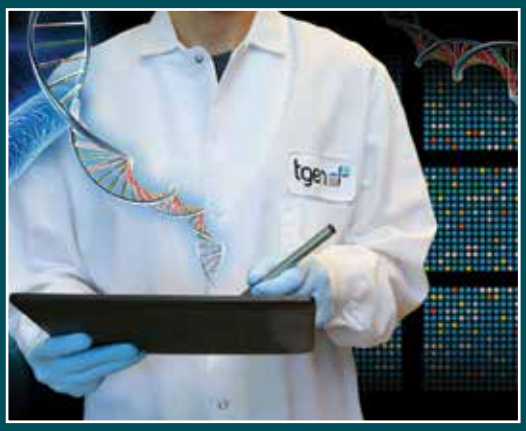
Fashion Fights Cancer at Key to the Cure

More than 200 fashionable women and men gathered at Saks Fifth Avenue in Phoenix for the 17th Annual Key to the Cure on October 16. ■ Co-chaired by Jacquie Dorrance and Katie Mueller, Key to the Cure featured a high-energy fashion show, gourmet breakfast, designer raffle items and a Diva Lounge. ■ "We have all been touched by the scourge of cancer," Mrs. Dorrance said. "Key to the Cure gathers so many wonderful people together to fund TGen's critical research." ■ This was the sixth year in a row that Saks has selected TGen's women's cancer research as the beneficiary of its Charity Shopping Weekend. ■ "We are honored that Saks has chosen to support TGen's groundbreaking research year after year," Mrs. Mueller explained. "The energy and excitement of Key to the Cure makes it a 'can't-miss' event on everyone's fall calendar." ■ On October 15, more than 100 discerning gentlemen gathered for the third annual Guys Night Out at Saks in support of prostate cancer research. ■ Together, the events raised more than $140,000.

Helios Scholars at TGen

Lab Skills to Life Skills: Helios Scholars at TGen turns 10

In 2016, Helios Scholars at TGen celebrates its 10th year of educating Arizona students through its hands-on internship program. Close to 400 high school, undergraduate and graduate students have participated, which was funded for 25 years through a $6.5 million award from the Helios Education Foundation. ■ Helios Scholars at TGen educates, trains and inspires the next generation of researchers and physicians in Arizona: ■ Claire Cambron, 2012-2013 Helios alumna and Arizona State University graduate; and Rachel Gur-Arie, 2014 Helios alumna and ASU student, were named 2015 Fulbright Scholars. ■ Shrey Gupta, 2013 Helios Scholar, earned the prestigious 2015 Coca-Cola Scholars Award. ■ Interns work side-by-side with TGen scientist-mentors. They learn laboratory skills and life skills. ■ "Getting to do real research in the lab was so important," said Divya Mahendra, a 2015 Helios Scholar. "You're helping the community with your work." ■ Applications for the 2016 Helios Scholars at TGen open January 5. For information, please contact Education and Outreach Specialist, Julie Euber at 602-343-8459 or jeuber@tgen.org.



TGen's Center for Non-Invasive Diagnostics

TGen seeks biomarkers for early detection, progression of Lou Gehrig's disease

The National Institutes of Health (NIH) has awarded a $687,087, one-year grant to TGen and Barrow Neurological Institute (BNI) to identify peptide, protein, and RNA biomarkers as indicators of Amyotrophic Lateral Sclerosis (ALS) progression. ■ This degenerative disease, also known as Lou Gehrig's disease, kills motor neurons – specialized nerve cells in the brain and spinal cord – causing progressive weakness and eventually death, usually in 3 to 5 years after diagnosis. No method of early detection exists for ALS, nor are there effective treatments – let alone a cure. ■ Identifying biomarkers that indicate early onset of ALS, and eventually pairing them with new treatments for patients in clinical trials, would be a major breakthrough. ■ Key to this study are recently proven methods led by TGen to identify extracellular RNA and conduct bioinformatic analysis of these pieces of genomic information from bodily fluids, including cerebral spinal fluid (CSF).

TGen, Riddell and ASU begin third year of concussion study

Riddell, the leader in football helmet technology and innovation, and TGen, a leader in cutting-edge genomic research, have begun the third year of a study to advance concussion detection and treatment with the Pac-12's Arizona State University and its Sun Devil football program. ■ Researchers are working to identify biomarkers released from the brain that provide definitive evidence of concussion. ■ The innovative study uses blood, saliva and urine samples collected from Sun Devil football student-athletes. ■ Select Sun Devils players' football helmets are equipped with sensors from the Riddell SRS to obtain real-time head impact data on the frequency and severity of head impacts experienced during games and practices. ■ Impacts are analyzed alongside genetic information from players that experience a concussion with the objective of helping physicians diagnose concussion and better identify when a player might be expected to recover and return to the field.

Select Sun Devils players' football helmets are equipped with sensors to obtain real-time head impact data

Upcoming Events Benefitting TGen:

To learn more about these events, please call the TGen Foundation at 602-343-8411 or visit: tgenfoundation.org/events

December 3-6, 2015
Wonderland Market *[Scottsdale, AZ]*
A holiday shopping extravaganza benefitting cancer research.
www.wonderlandmarket.com

January 23-31, 2016
Barrett-Jackson Collector Car Auction *[Scottsdale, AZ]*
Benefitting colon and prostate cancer research.
www.barrett-jackson.com

February 12, 2016
Focus on Lyme Fundraising Dinner *[Scottsdale, AZ]*
Proceeds will support trials of TGen's diagnostic test for Lyme disease.
www.focusonlyme.org

February 27, 2016
Roaring for Research, a 1920s themed soiree *[Phoenix, AZ]*
Casino games, jazz music, food and drinks in support of TGen's Center for Rare Childhood Disorders.
www.tgenfoundation.org/events

April 8-10, 2016
Barrett-Jackson Collector Car Auction *[Palm Beach, FL]*
Clarion Builds is donating its first project car, an iconic 1974 BMW 2002 restomod, to benefit colon and prostate cancer research at TGen.
www.barrett-jackson.com

April 9, 2016
2nd Annual Casey's Cup for ACC *[Anaheim, CA]*
A fun 3-on-3 ice hockey tournament for all age levels and abilities. It raises funds for Adrenocortical Cancer (ACC) research at TGen.
www.tgenfoundation.org/events

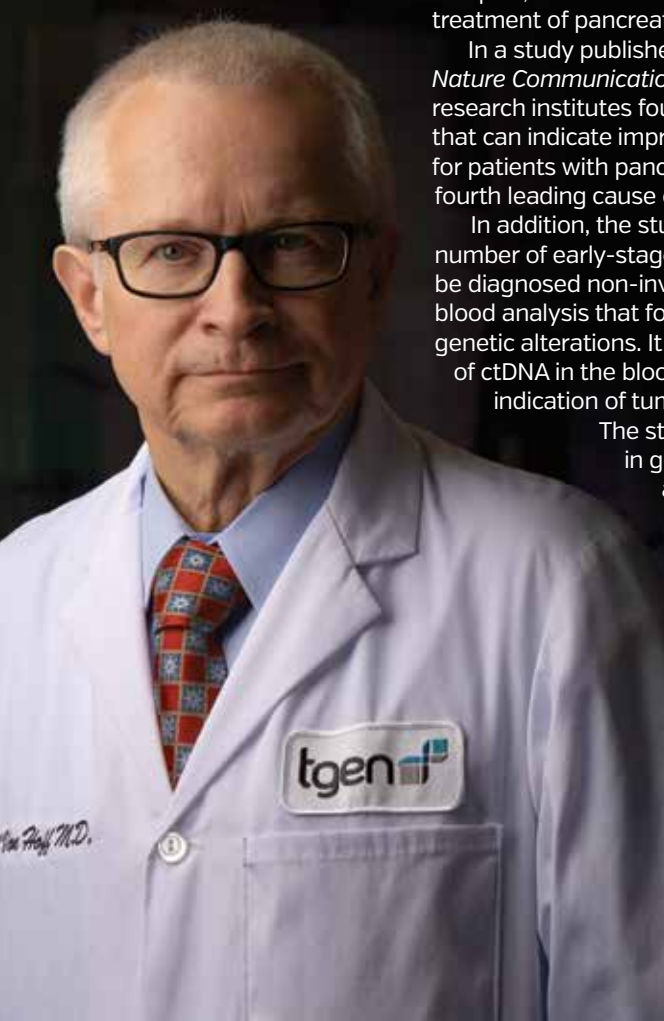
May 1, 2016
6th Annual Cycle for the Cure *[Phoenix, Scottsdale, Chandler, AZ]*
Enjoy a heart-pumping, high-energy indoor spin event at the Village Health Clubs, in support of cancer research.
www.tgenfoundation.org/events

Barrett-Jackson Collector Car Auction

Roaring for Research, a 1920s themed soiree

445 North Fifth Street, Suite 600
Phoenix, Arizona 85004

Pancreatic cancer study identifies genes associated with improved patient survival



Liquid biopsies, in which researchers look for circulating tumor DNA (ctDNA) in simple blood samples, could someday play a larger roll in the treatment of pancreatic cancer patients.

In a study published in July by the journal *Nature Communications*, TGen and other major research institutes found a new set of genes that can indicate improved survival after surgery for patients with pancreatic cancer, the nation's fourth leading cause of cancer-related deaths.

In addition, the study found that a significant number of early-stage pancreatic cancers could be diagnosed non-invasively using liquid biopsy blood analysis that focuses on a few specific genetic alterations. It showed that detection of ctDNA in the blood could provide an early indication of tumor recurrence.

The study identified mutations in genes MLL, MLL2, MLL3 and ARID1A in 20 percent of patients associated with improved survival. Using a liquid biopsy analysis, the study found that 43 percent of pancreatic cancer patients had ctDNA in their bloodstream at the time of diagnosis.

"We have identified MML genes as markers of improved prognosis for patients with pancreatic cancer," said Dr. Daniel D. Von Hoff, TGen Distinguished Professor, Physician-in-Chief, and one of the authors of the study. "We have also shown that ctDNA in the blood of pancreatic cancer patients may provide a marker of earlier detection of recurrence of the disease."

Very importantly, the study also found that detection of ctDNA following surgery predicts clinical relapse of the cancer and poor outcomes for patients. Using a liquid biopsy detected the recurrence of cancer 6.5 months earlier than using CT imaging.

"These observations provide predictors of outcomes in patients with pancreatic cancer and have implications for detection of tumor recurrence, and perhaps someday for early detection of the cancer," said Dr. Von Hoff, who also is Co-Director of TGen's Stand Up To Cancer (SU2C) Pancreatic Cancer Dream Team.

The pancreatic cancers analyzed in the study were stage II tumors from patients who underwent potentially curative surgery. Only 15-20 percent of patients are candidates for tumor resection, because pancreatic cancer is difficult to detect and usually is not diagnosed until its late stages when surgery is no longer an option. The 5-year survival rate for those diagnosed with pancreatic cancer is less than 10 percent.

Find out more about TGen pancreatic cancer research at: www.tgen.org/onemore.